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09/780,041	02/09/2001	Ronald Klein	UF-10293	8442

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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/780,041	KLEIN ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 August 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed March 24, 2003 has been entered. Claims 1-22 have been cancelled. Claims 23-38 have been newly added.

The supplemental response filed August 7, 2003 has been entered.

The Declaration filed August 7, 2003 is acknowledged.

It is noted that Claim 29 encompasses non-elected subject matter. However, Claim 29 is examined herein only to the extent that it encompasses the elected subject matter.

Claims 23-38 remain pending in the instant application.

Drawings

New corrected drawings are required in this application because Figures 3G-3K appear as black rectangles and do not show the features referred to in the specification. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

The drawings are objected to under 37 CFR 1.83(a) because Figures 3G-3K fail to show the features as described in the specification. Any structural detail that is essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d). A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: the claims recite the term "rodent" but the specification does not provide proper antecedent basis for the genus rodent.

Claim Objections

Claims 29, 32,and 37 are objected to because they cover non-elected subject matter. The elected invention is drawn to a method for producing a non-human animal model by transferring a gene encoding an aberrant form of tau, using somatic gene transfer techniques, a non-human animal comprising in its somatic cells a gene encoding an aberrant form of tau, and a method for inducing behavioral changes by somatic administration of a gene encoding an aberrant form of tau.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 23-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims introduce new matter into the application. The specification does not contemplate the genus of rodents. To provide support for the claim limitation "rodent", the specification must specifically contemplate that particular genus. However, nowhere does the specification describe the claimed invention as it applies to the general class of rodents. The Examiner has reviewed the specification and does not find specific support for this claim limitation. Thus, the claim amendments introduce new matter into the specification.

At pages 4 to 5 of the response, Applicants argue that one skilled in the art would understand, given the use of the terms non-human animal in conjunction with the terms rat and mice, that the application comprises implicit disclosure for the genus rodents. However, the term rodent is not used in the specification and therefore the use of the term in the claims is not supported by the specification as-filed.

Written Description

Claims 23-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants are referred to the final guidelines on written description published January 5, 2001 in the Federal Register at Volume 66, Number 4, pp. 1099-1111 (also available at www.uspto.gov).

The claims are directed to a method for producing a non-human animal model of a neurodegenerative disease by somatically transferring a gene encoding an aberrant form of tau protein into brain tissue of a living rodent under conditions which result in the expression of said gene, wherein expression of said gene results in a neuropathology in said living rodent corresponding to said neurodegenerative disease. Claims 34 and 35 are directed to compositions comprising a gene encoding an aberrant tau protein in a vector construct. These claims encompass animals comprising the gene.

However, the specification only describes genetically-modified rats that exhibit some features similar to those seen in Alzheimer's Disease. Additionally, the Declaration of Dr. Klein demonstrates that somatic genetic modification of mice also results in a phenotype similar to that seen in the rats. The claims are directed to a large genus of animals exhibiting any kind of phenotype associated with a disease of humans or other animals. However, the specification does not describe any other animal of the type claimed, wherein the animal exhibits a phenotype associated with a human or non-human animal disease. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In this case, since phenotype cannot be predicted for a genetically-modified animal for the reasons discussed herein below and no working examples describe a genetically-modified animal or the type claimed, other than a rat having a specific pathologic phenotype, no genetically-modified animals other than rats and mice have been described by their complete structure. Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. In this case, since phenotype cannot be predicted from the gene being introduced, no identifying characteristics are provided for genetically-modified dogs, pigs, primates, or any other animal. This limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of genetically-modified animals or rodents of the type claimed, other than rats and mice having the specific pathologic phenotype disclosed in the specification, at the time the application was filed. Thus, it is concluded that the written description requirement is not satisfied for the claimed genus, whether directed to animals or rodents.

Enablement

Claims 23-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (i) a method for producing a mouse or rat genetically modified by administration of a viral vector encoding a mutant form of human tau comprising the P301L mutation, wherein the mouse or

rat exhibits a neurofibrillary pathology as disclosed in the specification; (ii) a method for inducing behavioral changes in a mouse or rat by administration of a viral vector encoding a mutant form of human tau comprising the P301L mutation; and (iii) a viral vector adapted for *in vivo* expression in a mouse or rat brain tissue, said vector comprising a gene encoding a mutant form of human tau comprising the P301L mutation, does not reasonably provide enablement for the broad scope of animals produced by transferring a gene encoding an aberrant form of tau as claimed nor the methods for producing said animals. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification discloses rats that have been genetically modified by administration of an AAV vector encoding a mutant form of human tau (designated P301L tau in the specification). At page 14, lines 15-19, the specification discloses that the rats exhibit abnormal accumulation of tau in neuron cell bodies and dendrites, filaments immunoreactive for hyperphosphorylated tau, neuritic immunoreactivity for several antibodies that recognized neurofibrillary tangles in Alzheimer's and FTDP-17, and a dramatic increase of reactive astrogliosis.

The specification fails to provide an enabling disclosure for the preparation of the full scope of genetically-modified animals or rodents as claimed exhibiting an appropriate phenotype, other than genetically-modified rats and mice, because the phenotype of a genetically-modified animal cannot be predicted.

The specification fails to provide an enabling disclosure for the preparation of any species of genetically modified animal harboring a gene encoding an aberrant form of tau because the guidance offered in the specification is not sufficient to teach one of skill in the art how to prepare the claimed genetically modified animals exhibiting an appropriate phenotype, other than rats and mice. The mere capability to perform gene transfer in any given species is not enabling for the claimed genetically-

modified animals and methods of producing them because the desired phenotype cannot be predictably achieved by simply introducing a construct as recited in the claims. While gene transfer techniques are well-developed for a variety of species, methods for achieving the desired level of transgene expression in appropriate tissues are less well-established. With regard to transgenic animals, the introduction of DNA into the mammalian genome can ordinarily be achieved most reliably by microinjection or retrovirus-mediated gene transfer. However, the state of the art for transgenics and other *in vivo* genetic modifications is unpredictable because the method of gene transfer typically relies on random integration of the transgene construct or no integration. When random integration occurs, insertional inactivation of endogenous genes and position effects (see Wall, 1996, p. 61, paragraph 3) can dramatically influence the phenotype of the resultant genetically-modified animal. Integration of the transgene near highly active genes or, alternatively, in a transcriptionally inactive region, can influence its level of expression. Furthermore, expression of the transgene and the effect of transgene expression on the phenotype of the genetically-modified animal depends on the particular gene construct used, to an unpredictable extent. The particular genetic elements required for appropriate expression varies from species to species. Thus, a construct that confers the desired phenotype in a rat cannot necessarily achieve the same result in a mouse. Wall (1996) reports that our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (p. 61, paragraph 3). This is especially relevant for species in which genetic studies are less advanced than in the mouse. Thus, the species-specific requirements for transgene design introduces an additional level of unpredictability associated with the development of genetically-modified animals. Even differences in the genetic background of transgenic mice can have an unpredictable effect on phenotype (Sigmund, 2000). In the absence of specific guidance, the production of a transgene-dependent phenotypic alteration resulting from the introduction of a nucleic acid construct as recited in the claim, is unpredictable. Thus, given the limited working examples directed exclusively to genetically-modified rats, and the post-filing results directed to

genetically-modified mice, the existence of any phenotypic alteration resulting from the introduction of a gene encoding an aberrant form of tau in any species of the animal kingdom other than rats and mice, is highly unpredictable. Given the limited working examples and the unpredictability in the art, one of ordinary skill in the art would have been required to engage in undue experimentation in order to make and use the claimed genetically-modified animals or rodents over the full scope.

The species-specific requirements for transgene design are not clearly understood. Examples in the literature aptly demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. For example, several animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins et al. (1990) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer et al. (1990) describe spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice (Mullins et al., 1989; Taurog et al., 1988) expressing the same transgenes that successfully caused the desired symptoms in transgenic rats.

Houdebine (1994) discloses that in the field of transgenics, constructs must be designed case by case, without general rules, to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (page 275, column 1, paragraph 1). Wall (1996) discloses the unpredictability of transgene behavior due to factors such as position effect and unidentified control elements, and may result in a lack of transgene expression or variable expression (paragraph bridging pages 61-62). Additionally, Kappel et al. (1992) disclose the existence of inherent cellular mechanisms that may alter the pattern of gene expression such as DNA imprinting, resulting from differential CpG methylation (page 549, column 2, paragraph 4). The level of skill in the art of *in vivo* genetic modification is such that one cannot predict whether a transgene that is expressed in a mouse will also be expressed efficiently in another animal. For

example, Strojek and Wagner (1988) point out that a high degree of expression of a transgene in a mouse is often not predictive of high expression in other species, including pigs and rabbits, because, for example, the cis-acting elements may interact with different trans-acting factors in these other species (paragraph bridging pages 238-239). Furthermore, Wall (1996) explicitly teaches that transgene expression and the physiological consequences of transgene expression are not always accurately predicted in transgenic mouse studies (page 62, paragraph 1).

Given that specific phenotypic alterations cannot be predictably achieved by merely transferring a gene of interest into an animal, specific guidance must be provided to enable the instant invention over the full scope. The specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. The claims cover the use of the genetically-modified animals as a model for Alzheimer's Disease, but the specification does not enable this use for any animal other than rats. The claims also cover the use of genetically-modified animals expressing an aberrant form of tau as a model for Huntington's Disease, but the specification does not enable this use for any animal species. In the absence of specific guidance for making and using genetically-modified animals other than rats and mice exhibiting an appropriate phenotype, undue experimentation would have been required to make and use the full scope of the claimed animals (or rodents) and practice the claimed methods over the full scope.

Accordingly, given the demonstrated lack of predictability in the art, the limited amount of direction given, the state of the prior art, the quantity of experimentation needed, and the limited applicable working examples, one of skill in the art would not be able to make and use the claimed invention over the full scope without undue experimentation.

The Declaration of Dr. Ronald Klein, filed August 7, 2003, has been fully considered and is found to be partially persuasive. Thus, the scope of enablement has been expanded to include somatic genetic modification of mice as well as rats.

At page 5 of the response, Applicants assert that there is no scientific rationale for why the same phenotypes generated in rats cannot also be produced in mice and other rodents. However, ample scientific rationale has been provided, supported by 9 references, for concluding that the phenotype of a genetically-modified animal is unpredictable. For the reasons discussed above, the results obtained in mice and rats are not considered to be predictive of the larger genus of rodents.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23-28 and 34-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to -particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 23-28 and 34-38 are indefinite in their recitation of "non-human animal" and/or "living animal" within the same claim that recites "living rodent." A broad limitation together with a narrow limitation that falls within the broad limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims 23-28 and 34-38 recites the broad recitation "non-human animal" and/or "living animal", and the claim also recites "living rodent" which is the narrower statement of the limitation.

Claim 35 is indefinite in its recitation of "said aberrant tau protein is P301L" because the term "P301L" refers to a specific amino acid mutation and thus, an aberrant tau protein cannot be a single amino acid mutation.

Claim 35 is indefinite in its recitation of "P301L" because no reference sequence is provided and therefore it is unclear what numbering system is being used and which residue of tau is being referred to.

Claim 37 is indefinite in its recitation of "said living rodent" because the phrase lacks antecedent basis.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, William Phillips, whose telephone number is (703) 305-3482.

Anne-Marie Falk, Ph.D.

Anne-marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER